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(54) Title: NOVEL PROCESS

(57) Abstract: The invention relates to a novel process for the preparation of substituted indoles which are useful as therapeutic agents.

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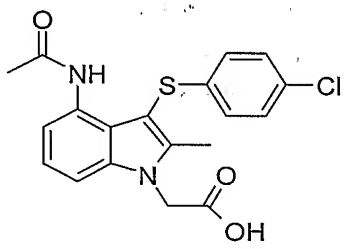
NOVEL PROCESS

The present invention relates to a novel process for the preparation of substituted indoles which are useful as therapeutic agents.

WO 04/106302 discloses a series of substituted indoles useful for the treatment of respiratory diseases.

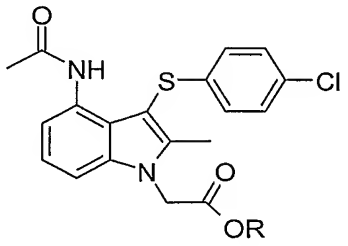
New processes have now been developed for certain compounds which are more efficient than those disclosed in the art.

In a first aspect the invention therefore provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



(I)

which comprises de-esterification of a compound of formula (II):



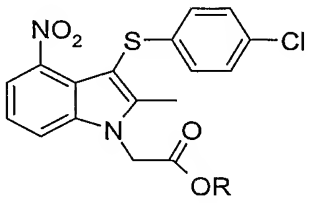
(II)

in which R is an ester forming group, and optionally thereafter forming a pharmaceutically acceptable salt or solvate.

The reaction can be carried out in the presence of a base followed by treatment with acid and a ketone or ester containing solvent or mixtures of said solvents or mixtures comprising said solvents. The compounds of formula (II) are treated with a base such as an alkali metal hydroxide in a suitable solvent such as an organic alcohol, preferably at elevated temperature. The reaction mixture is then treated with acid at elevated temperature in the

presence of ketone or ester-containing solvents to give the compound of formula (I). The use of ketone and ester-containing solvents has surprisingly been found to promote crystal growth. Suitable solvents include ethyl acetate, n-propylacetate and MIBK and mixtures thereof. Preferably MIBK is used. Preferably the compound of formula (II) is treated with aqueous sodium hydroxide in n-propanol at elevated temperature, for example at about 68°C. Preferably the group R is phenyl, benzyl or a C_{1-6}alkyl group such as methyl or ethyl, preferably R is C_{1-6}alkyl, more preferably ethyl.

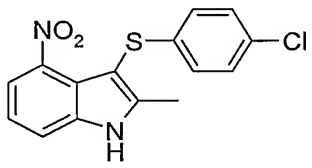
Compound of formula (II) are prepared by reaction of compounds of formula (III):



(III)

in which R is hydrogen or is as defined in formula (II) by hydrogenation followed by treatment of the resulting amine with an acetylating agent such as acetyl chloride. Preferably R is an ester forming group as defined in formula (II). The hydrogenation can be carried out using standard conditions such as using a platinum catalyst under a hydrogen atmosphere at elevated pressure, e.g. a pressure of about 4 bar. This reduction can also be achieved with sodium dithionite. The resulting amine, which is optionally isolated, for example by crystallisation from ethyl acetate/iso-hexane, is treated with acetyl chloride in a solvent such as ethyl acetate at ambient or elevated temperature, preferably at about 40°C.

Compounds of formula (III) can be prepared by reacting compounds of formula (IV):



(IV)

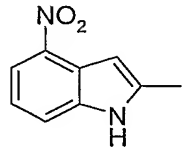
with compounds of formula (V):

$$XCH_2CO_2R$$

(V)

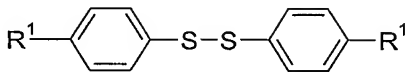
in which R is as defined in formula (II) and X is halogen. Preferably R is ethyl and X is bromo such that the compound (V) is ethylbromoacetate. The reaction is carried out in the presence of a base such as potassium carbonate in water/acetonitrile.

Compounds of formula (IV) can be prepared by reacting compounds of formula (VI):



(VI)

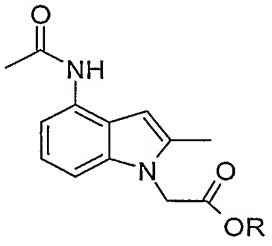
with compounds of formula (VII):



(VII)

in which R^1 is chloro or a group that be converted to chloro such as amino or hydrogen. Preferably R^1 is chloro. The reaction of compounds (VI) and (VII) can be carried out using a suitable base such as sodium methoxide in methanol at elevated temperature, or a reagent such as trichloroisocyanuric acid in a solvent such as ethyl acetate or dichloromethane.

In an alternative embodiment of the invention compounds of formula (II) can be prepared from compounds of formula (VIII):

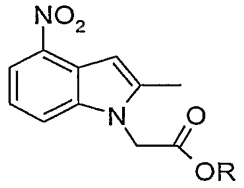


(VIII)

in which R is hydrogen or is as defined in formula (II) by reacting with a compound of formula (VII). The reaction can be carried out using trichloroisocyanuric acid as described

above. This reaction is advantageous where R is hydrogen as it can be used for the direct preparation of compounds of formula (I).

Compounds of formula (VIII) can be prepared from compounds of formula (IX):



(IX)

in which R is hydrogen or is as defined in formula (II) by hydrogenation and subsequent reaction of the resulting amine using analogous conditions to those described above for the hydrogenation of compound (V). Preferably R is as defined in formula (II), more preferably R is ethyl.

Compound (IX) can be prepared from a compound of formula (VI) by reaction with a compound such as ethylbromoacetate using analogous conditions to those described above for the reaction of compound (IV).

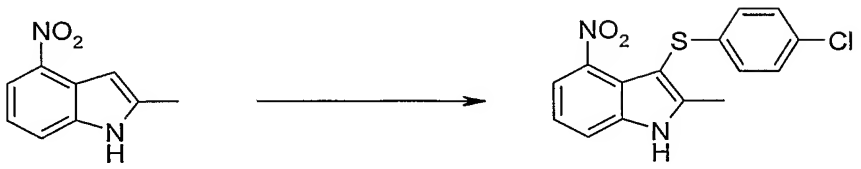
In a still further embodiment of the invention compounds of formula (III) can be prepared from compounds of formula (IX) as defined above by reacting with a compound of formula (VII) as defined above using analogous conditions to those described above for the reaction of compounds (VI) and (VII) using TCCA.

All novel intermediates disclosed herein form a further aspect of the invention. In a further aspect the invention therefore provides a compound of formula (VIII) and (IX).

The following examples illustrate the invention.

Example 1

3-(4-Chlorophenylsulfanyl)-2-methyl-4-nitro-1*H*-indole



Method A

Sodium methoxide in methanol (4.1 kg, 25% *w/w*, 19 mol) was added to a stirred suspension of 2-methyl-4-nitro-1*H*-indole (1.52 kg, 8.6 mol) and *bis*(p-chlorophenyl)disulphide (2.48 kg, 8.6 mol) in methanol (6.47 kg) followed by a methanol line rinse (0.67 kg). The mixture was then heated at 60 – 65 °C for 3.5 hours. Water (6.1 kg) was added to the reaction mixture, which was then cooled to 20 °C and stirred at this temperature for 7 minutes. The solid was collected by filtration, washed with water (2 x 4 kg) followed by ethyl acetate (2 x 4 kg) then dried in a vacuum oven at 40 °C. 3-(4-Chlorophenylsulfanyl)-2-methyl-4-nitro-1*H*-indole was obtained as a bright yellow solid, 2.57 kg (93% yield).

^{1}H NMR (400 MHz, D_6-DMSO) δ 7.77 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.27 (m, 3H), 6.92 (d, J = 8.8 Hz, 2H), 2.48 (s, 3H).

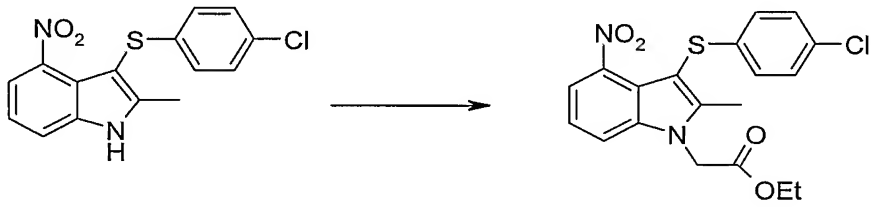
LC-MS (ES^+): 319 (100%, MH^+).

Method B

Trichloroisocyanuric acid (450 mg, 1.9 mmol) was added to a solution of *bis*(p-chlorodiphenyl)disulphide (1.63 g, 5.7 mmol) in ethyl acetate (10 ml) at ambient temperature, resulting in the formation of an orange suspension. After stirring at ambient temperature for 30 minutes, a suspension of 2-methyl-4-nitro-1*H*-indole (2.0 g, 11.3 mmol) in ethyl acetate (10 ml) was added followed by an ethyl acetate rinse (4 ml), using water bath cooling to control the mild exotherm. Stirring was continued at ambient temperature for 40 minutes. Aqueous sodium bicarbonate (5%, 20 ml) and water (20 ml) were added and the resulting suspension stirred at ambient temperature for 45 minutes. The solid was collected by

filtration, washed with water (2 x 10 ml), followed by ethyl acetate (2 x 10 ml) then dried in a vacuum oven at 45 °C to provide 3-(4-chlorophenylsulfanyl)-2-methyl-4-nitro-1*H*-indole, 2.9 g (81%) as a yellow / brown solid.

[3-(4-Chlorophenylsulfanyl)-2-methyl-4-nitro-1*H*-indol-1-yl]acetic acid, ethyl ester: method A

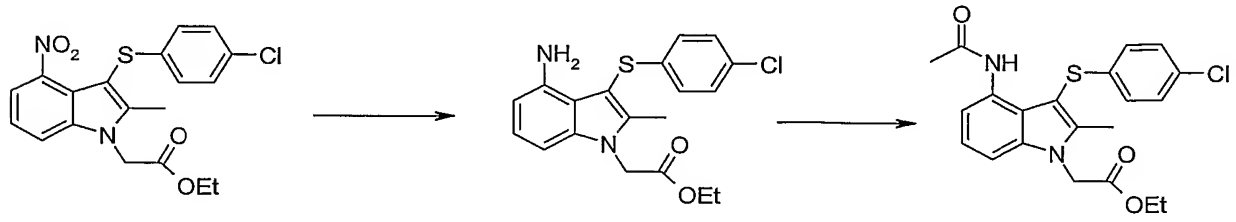


3-(4-Chlorophenylsulfanyl)-2-methyl-4-nitro-1*H*-indole (3.76 kg, 11.8 mol) and potassium carbonate (1.80 kg, 13.0 mol) were suspended in acetonitrile (32.7 kg). Water (0.53 kg) and a solution of ethyl bromoacetate (2.17 kg, 13.0 mol) in acetonitrile (5.75 kg) were added followed by an acetonitrile line rinse (2.97 kg). The mixture was heated at 50 °C for 6 hours then allowed to cool to 20 °C and held at this temperature overnight. Water (35.4 kg) was added to the reaction mixture and stirring continued for 30 minutes at 15 °C. The solid product was collected by filtration, washed with acetonitrile (2.95 kg) then dried in a vacuum oven at 40 °C to afford [3-(4-chlorophenylsulfanyl)-2-methyl-4-nitro-1*H*-indol-1-yl]acetic acid, ethyl ester as a bright yellow solid, 4.33 kg (91%).

^{1}H NMR (300 MHz, D_6-DMSO) δ 7.97 (dd, J = 8.3, 0.8 Hz, 1H), 7.65 (dd, J = 7.9, 0.8 Hz, 1H), 7.34 (t, J = 8.1 Hz, 1H), 7.26 (m, 2H), 6.92 (m, 2H), 5.40 (s, 2H), 4.19 (q, J = 7.0 Hz, 2H), 2.45 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H).

LC-MS (ES^+): 405 (100%, MH^+), 407 (MH^+).

[4-Acetylamino-3-(4-chlorophenylsulfanyl)-2-methyl-1*H*-indol-1-yl]acetic acid, ethyl ester: method A

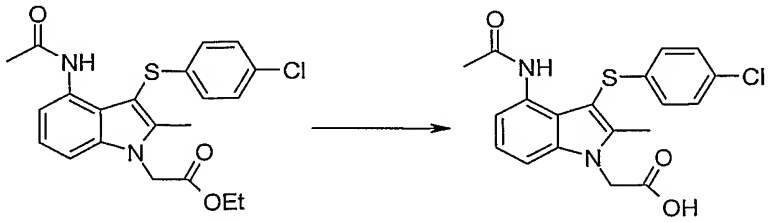


A solution of [3-(4-chlorophenylsulfanyl)-2-methyl-4-nitro-1*H*-indol-1-yl]acetic acid, ethyl ester (1.99 kg, 4.92 mol) in ethyl acetate (24.2 kg) was hydrogenated in the presence of a 1% Pt / C catalyst paste (1.39 kg 44% *w/w*) under 4 bar A hydrogen pressure. After 2 hours hydrogen uptake had ceased so the reaction mixture was inerted then filtered through Celite (2.60 kg). The solids were washed with ethyl acetate (3 x 8 kg) and the combined filtrates distilled until a volume of 26 L remained to leave a solution of [4-amino-3-(4-chlorophenylsulfanyl)-2-methylindol-1-yl]acetic acid, ethyl ester in ethyl acetate. This solution was cooled to 4 °C then triethylamine (0.50 kg, 4.94 mol) added, followed by an ethyl acetate line wash (0.82 kg). A solution of acetyl chloride (0.39 kg, 4.97 mol) in ethyl acetate (3 kg) was added followed by an ethyl acetate line wash (0.76 kg). The reaction mixture was heated at 40 °C for 17 hours then water (16.9 kg) added. The reaction mixture was distilled down until 24.6 kg of distillate had been removed then cooled to 20 °C. The solid product was collected by filtration, washed with water (1.9 kg) followed by acetonitrile (1.6 kg) then dried in a vacuum oven at 40 °C to afford [4-acetylamino-3-(4-chlorophenylsulfanyl)-2-methyl-1*H*-indol-1-yl]acetic acid, ethyl ester, 1.69 kg (82%) as an off white solid.

^{1}H NMR (300 MHz, DMSO) δ 9.51 (s, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.36 - 7.25 (m, 3H), 7.11 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 8.7 Hz, 2H), 5.24 (s, 2H), 4.18 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.86 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H).

LC-MS (ES^+): 417 (100%, MH^+), 419 (MH^+).

[4-Acetylamino-3-(4-chlorophenylsulfanyl)-2-methyl-1*H*-indol-1-yl]acetic Acid

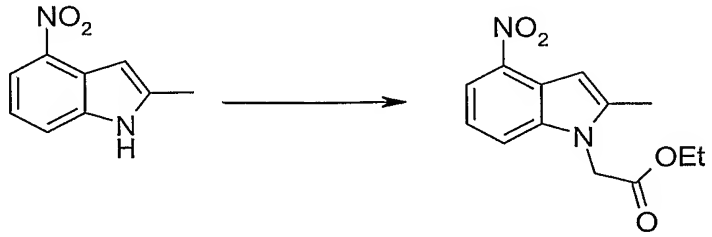


Aqueous sodium hydroxide (1 M, 11.7 kg) was added to a solution of [4-acetylamino-3-(4-chlorophenylsulfanyl)-2-methyl-1*H*-indol-1-yl]acetic acid, ethyl ester (2.20 kg, 5.28 mol) in 1-propanol (8.2 kg) and the mixture heated to 68 °C. After cooling to 40 °C, the solution was filtered, the filter rinsed with water (1 kg) then methyl *iso*butyl ketone (17.8 kg) was added to the filtrate, which was re-heated to 80 °C. Aqueous hydrochloric acid (1 M, 12.2 kg) was added over a period of 90 minutes then the mixture cooled to 19 °C. The crystalline solid was collected by filtration, washed with water (2 x 4 kg), ethyl acetate (6 kg) then dried in a vacuum oven at 40 °C to provide [4-acetylamino-3-(4-chlorophenylsulfanyl)-2-methyl-1*H*-indol-1-yl]acetic acid as white crystals, 1.87 kg (91%).

^{1}H NMR (400 MHz, D_6-DMSO) δ 9.51 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.38 - 7.24 (m, 3H), 7.11 (t, J = 8.1 Hz, 1H), 6.98 (d, J = 8.5 Hz, 2H), 5.12 (s, 2H), 2.40 (s, 3H), 1.86 (s, 3H).

LC-MS (ES^+): 389 (100%, MH^+), 391 (MH^+).

(4-Nitro-2-methyl-1*H*-indol-1-yl)-acetic acid, ethyl ester



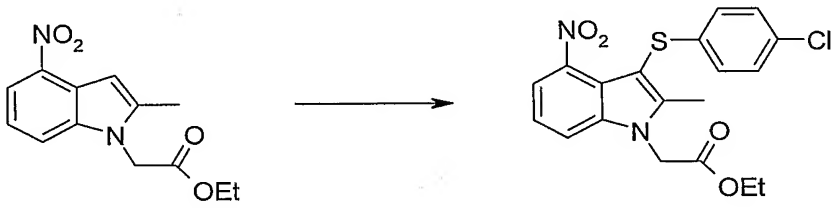
Water (4.5 ml), potassium carbonate (25.9 g, 187 mmol) and ethyl bromoacetate (20.8 ml, 188 mmol) were added sequentially to a suspension of 2-methyl-4-nitro-1*H*-indole (30 g, 170 mmol) in acetonitrile (225 ml) and the mixture heated at 60 °C for 16 hours. After allowing to cool to ambient temperature, water (225 ml) was added and the resulting mixture

was broken up and then filtered. The solid was washed with water (2 x 75 ml), followed by IMS (2 x 75 ml) then dried in a vacuum oven to give (4-nitro-2-methyl-1*H*-indol-1-yl)-acetic acid, ethyl ester, 32.15 g (72%).

^{1}H-NMR (300 MHz, D_6-DMSO) δ 8.04 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.27 (t, J = 8.1 Hz, 1H), 6.93 (s, 1H), 5.25 (s, 2H), 4.17 (q, J = 7.1 Hz, 2H), 2.44 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H)

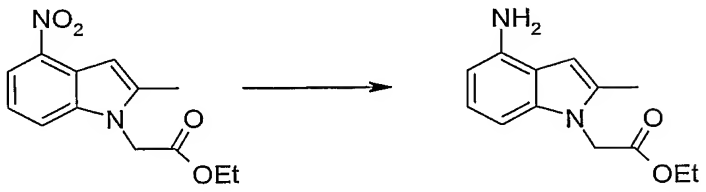
LC-MS (ES^+): 263 (100%, MH^+)

[3-(4-Chlorophenylsulfanyl)-2-methyl-4-nitro-1*H*-indol-1-yl]acetic acid, ethyl ester: method B



Trichloroisocyanuric acid (0.30 g, 1.3 mmol) was added to a solution of *bis*(p-chlorophenyl)disulphide (1.08 g, 3.8 mmol) in ethyl acetate (10 ml) at ambient temperature resulting in formation of a yellow suspension. After stirring for 30 minutes at this temperature, a slurry of (4-nitro-2-methyl-1*H*-indol-1-yl)-acetic acid, ethyl ester (2.0 g, 7.6 mmol) in ethyl acetate (10 ml) was added followed by an ethyl acetate rinse (4 ml), using water bath cooling to control the mild exotherm. Stirring was continued for 35 minutes at ambient temperature. Aqueous sodium bicarbonate (5%, 20 ml) was added followed by water (20 ml). After stirring for 45 minutes, ethyl acetate was removed by evaporation, the solid product collected by filtration, washed with water (2 x 10 ml), followed by 50% *v/v* aqueous acetonitrile (2 x 10 ml) then dried overnight in a vacuum oven at 45 °C to provide [3-(4-chlorophenylsulfanyl)-2-methyl-4-nitro-1*H*-indol-1-yl]acetic acid, ethyl ester as a bright yellow solid, 2.95 g (96%).

(4-Amino-2-methyl-1*H*-indol-1-yl)-acetic acid, ethyl ester

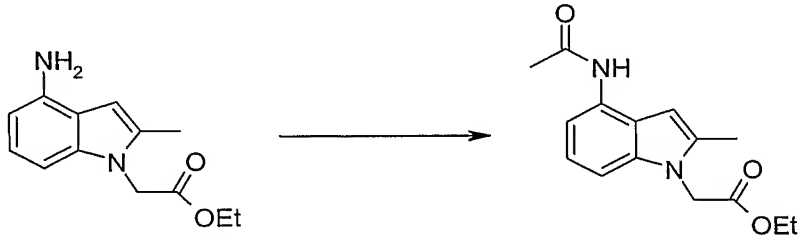


A solution of (4-nitro-2-methyl-1*H*-indol-1-yl)-acetic acid, ethyl ester (5.0 g, 19 mmol) in ethyl acetate (75 ml) was hydrogenated under 3 bar hydrogen pressure in the presence of a wet 1% Pt / C catalyst paste (38 *w/w*, 0.7 g) until hydrogen uptake ceased (3 hours). The reaction mixture was filtered through kieselguhr and the solids washed with ethyl acetate (75 ml). The filtrate and wash were combined with solutions obtained from 2 previous experiments which had been carried out in a similar manner, each on a 2 g scale, and evaporated to dryness to provide (4-amino-2-methyl-1*H*-indol-1-yl)-acetic acid, ethyl ester, 8.59 g, >100% as a brown oil which solidified on standing.

^{1}H NMR (300 MHz, D_6-DMSO) δ 6.73 (t, J = 7.9 Hz, 1H), 6.49 (d, J = 8.1 Hz, 1H), 6.28 (s, 1H), 6.15 (d, J = 7.5 Hz, 1H), 5.05 (br s, 2H), 4.89 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 2.27 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H).

LC-MS (ES^+): 233 (100%, MH^+).

(4-Acetylamino-2-methyl-1*H*-indol-1-yl)-acetic acid ethyl ester



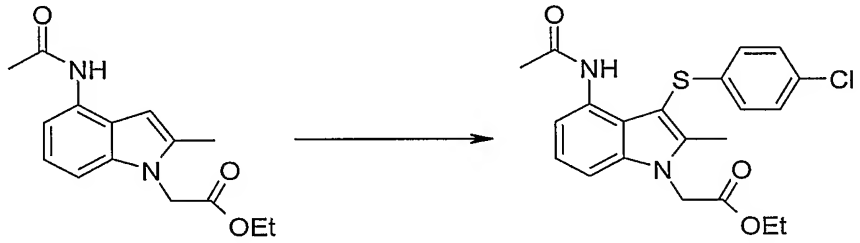
The (4-amino-2-methyl-1*H*-indol-1-yl)-acetic acid, ethyl ester prepared above (8.59 g) was dissolved in ethyl acetate (175 ml) then triethylamine (5.2 ml, 37 mmol) added followed by acetyl chloride (2.6 ml, 37 mmol). An exotherm to 35 °C was observed and a thick suspension resulted. After stirring for 4 hours during which the mixture was allowed to cool back to ambient temperature, water (85 ml) was added and the ethyl acetate removed by

evaporation under vacuum. The solid was collected by filtration, washed with water (25 ml) followed by 50% *v/v* aqueous acetonitrile (50 ml) then dried in a vacuum oven at 50 °C overnight to provide (4-acetylamino-2-methyl-1*H*-indol-1-yl)-acetic acid, ethyl ester, as an off-white solid, 7.26 g (77% from (4-nitro-2-methyl-1*H*-indol-1-yl)-acetic acid, ethyl ester).

^{1}H NMR (300 MHz, D_6-DMSO) δ 9.51 (s, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 6.96 (t, J = 7.9 Hz, 1H), 6.50 (s, 1H), 5.02 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 2.33 (s, 3H), 2.12 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H).

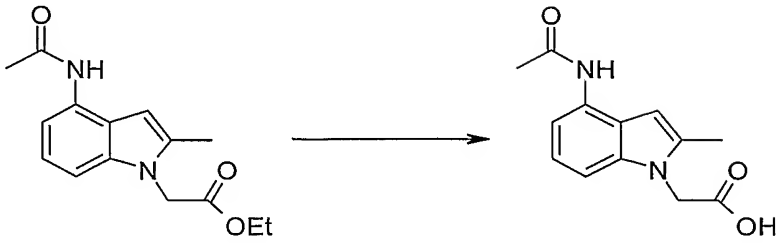
LC-MS (ES^+): 275 (100%, MH^+).

[4-Acetylamino-3-(4-chloro-phenylsulfanyl)-2-methyl-1*H*-indol-1-yl]-acetic acid, ethyl ester: method B



Trichloroisocyanuric acid (0.15 g, 0.65 mmol) was added to a solution of *bis*(p-chlorophenyl)disulphide (0.55 g, 1.9 mmol) in ethyl acetate (5.25 ml) at ambient temperature resulting in formation of a yellow suspension. After stirring for 15 minutes at this temperature, a slurry of (4-acetylamino-2-methyl-1*H*-indol-1-yl)-acetic acid, ethyl ester (1.05 g, 3.8 mmol) in ethyl acetate (5.25 ml) was added, followed by an ethyl acetate rinse (2 ml), using water bath cooling to control the mild exotherm. Stirring was continued for 1h 15 minutes at ambient temperature. Aqueous sodium bicarbonate (5%, 10.5 ml) was added followed by water (10.5 ml). After stirring for 35 minutes, the solid product was collected by filtration, washed with water (2 x 5 ml) then dried in a vacuum oven at 45 °C overnight to give [4-acetylamino-3-(4-chlorophenylsulfanyl)-2-methyl-1*H*-indol-1-yl]-acetic acid, ethyl ester as a grey solid, 1.13 g, 71%).

(4-Acetylamino-2-methyl-1*H*-indol-1-yl)acetic acid

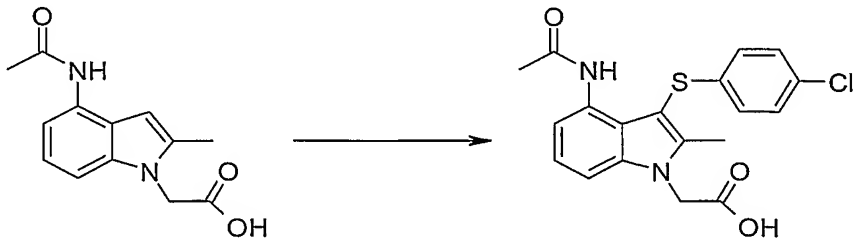


(4-Acetylamino-2-methyl-1*H*-indol-1-yl)-acetic acid, ethyl ester (2.0 g, 7.3 mmol) was slurried in ethanol (10 ml) at ambient temperature. Aqueous sodium hydroxide (1 M, 10 ml, 10 mmol) was added and the mixture heated to 50 °C. The solution obtained at was then allowed to cool back to ambient temperature and aqueous hydrochloric acid (1 M, 11 ml, 11 mmol) added. The resulting solid was collected by filtration, washed with water (2 x 10 ml) then dried in a vacuum oven at 45 °C overnight to provide (4-acetylamino-2-methyl-1*H*-indol-1-yl)acetic acid as an off-white solid, 1.66 g (92%).

^{1}H NMR (300 MHz, D_6-DMSO) δ 12.97 (s, 1H), 9.49 (s, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 6.95 (t, J = 7.9 Hz, 1H), 6.49 (s, 1H), 4.91 (s, 2H), 2.33 (d, J = 0.8 Hz, 3H), 2.12 (s, 3H)

LC-MS (ES^+): 247 (100%, MH^+).

[4-Acetylamino-3-(4-chlorophenylsulfanyl)-2-methyl-1*H*-indol-1-yl]acetic Acid: method B

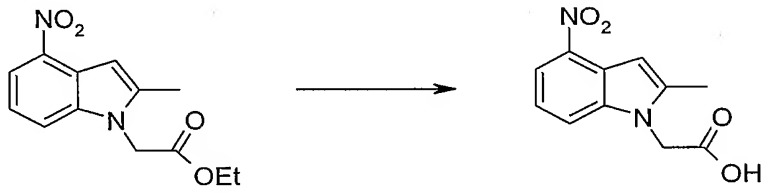


Trichloroisocyanuric acid (0.13 g, 0.56 mmol) was added to a solution of *bis*(p-chlorophenyl)disulphide (0.47 g, 1.6 mmol) in ethyl acetate (5 ml) at ambient temperature resulting in formation of a yellow suspension. After stirring for 15 minutes at this

temperature, a slurry of (4-acetylamino-2-methyl-1*H*-indol-1-yl)acetic acid (0.80 g, 3.2 mmol) in ethyl acetate (10 ml) was added followed by an ethyl acetate rinse (5 ml), using water bath cooling to control the mild exotherm. Stirring was continued for 1 h 15 minutes at ambient temperature. The solid product was collected by filtration, washed with ethanol (2 x 10 ml) then dried overnight in a vacuum oven at 45 °C to provide [4-acetylamino-3-(4-chlorophenylsulfanyl)-2-methyl-1*H*-indol-1-yl]acetic acid as an off-white solid, 1.22 g (97%).

Example 2

(2-Methyl-4-nitro-1*H*-indol-1-yl)acetic acid

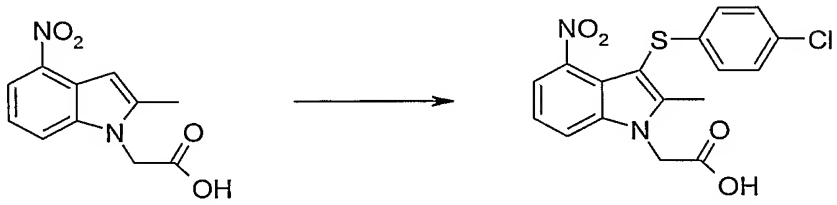


Aqueous sodium hydroxide (1 M, 25 ml) was added to a solution of (4-nitro-2-methyl-1*H*-indol-1-yl)acetic acid, ethyl ester (5.0 g, 18.9 mmol) in ethanol (25 ml) and the mixture warmed to 40 °C. After stirring for 70 mins at this temperature, the mixture was allowed to cool back to ambient temperature and aqueous hydrochloric acid (1 M, 27.5 ml) added causing precipitation of a solid. This was collected by filtration, washed with water (2 x 25 ml) then dried in a vacuum oven at 50 °C overnight to leave (2-methyl-4-nitro-1*H*-indol-1-yl)acetic acid as a yellow solid, 4.18 g (94%).

^{1}H-NMR (300 MHz, D_6-DMSO) δ 13.2 (s, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.26 (t, J = 8.1 Hz, 1H), 6.92 (s, 1H), 5.13 (s, 2H), 2.45 (s, 3H)

LC-MS (ES^+): 235 (100%, MH^+)

[3-(4-Chlorophenylsulfanyl)-2-methyl-4-nitro-1*H*-indol-1-yl]acetic acid



Trichloroisocyanuric acid (0.51 g, 2.2 mmol) was added to a solution of *bis*(*p*-chlorophenyl)disulphide (1.84 g, 6.4 mmol) in ethyl acetate (15 ml) at ambient temperature resulting in formation of a yellow suspension. After stirring for 5 minutes at this temperature, a slurry of (4-nitro-2-methyl-1*H*-indol-1-yl)-acetic acid (3.0 g, 12.8 mmol) in ethyl acetate (30 ml) was added followed by an ethyl acetate rinse (6 ml). Stirring was continued for 40 minutes at ambient temperature. The solid product was collected by filtration, washed with ethyl acetate (2 x 10 ml) then dried overnight in a vacuum oven at 50 °C to provide [3-(4-chlorophenylsulfanyl)-2-methyl-4-nitro-1*H*-indol-1-yl]acetic acid as a bright yellow solid, 2.93 g. The by-product, cyanuric acid, was not removed during the work up.

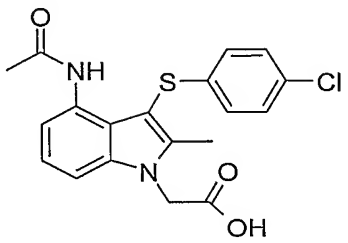
^{1}H NMR (300 MHz, D_6-DMSO) δ 13.4 (s, 1H), 7.97 (dd, J = 8.3, 0.8 Hz, 1H), 7.64 (dd, J = 7.7, 0.8 Hz, 1H), 7.34 (t, J = 8.1 Hz, 1H), 7.25 (m, 2H), 6.92 (m, 2H), 5.28 (s, 2H), 2.45 (s, 3H).

LC-MS (ES^+): 377 (100%, MH^+), 379 (MH^+).

The product can be converted to a compound of formula (I) by reduction of the nitro group followed by amide formation using a process analogous to that given above for [4-Acetylamino-3-(4-chlorophenylsulfanyl)-2-methyl-1*H*-indol-1-yl]acetic acid, ethyl ester: method A

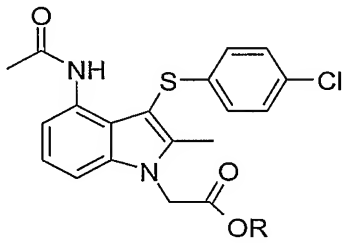
Claims

1. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



(I)

which comprises de-esterification of a compound of formula (II):



(II)

in which R is an ester forming group, in the presence of a base followed by treatment with an acid and a ketone or ester containing solvent, and optionally thereafter forming a pharmaceutically acceptable salt or solvate.

2. A process according to claim 1 in which R is C_{1-6}alkyl.

3. A process according to claim 1 or 2 in which R is ethyl.

4. A process according to any one of claims 1 to 3 which is carried out using an alkali metal hydroxide in an organic alcohol solvent.

5. A process according to any one of claims 1 to 4 which is carried out using aqueous sodium hydroxide in n-propanol.

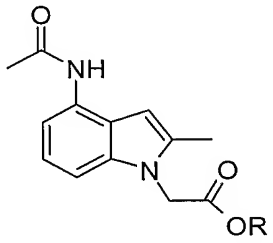
6. A process according to any one of claims 1 to 5 which is carried out at a temperature of about 68°C.

7. A process according to any one of claims 1 to 5 in which the acid treatment is carried out in the presence of ethyl acetate, n-propylacetate and MIBK and mixtures thereof.

8. A process according to any one of claims 1 to 5 which the acid treatment is carried out in the presence of MIBK.

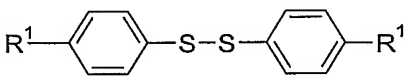
9. A compound of formula (I) prepared using the process according to any one of claims 1 to 8.

10. A process for the preparation of a compound of formula (I) or (II) which comprises reaction of a compound of formula (VIII):



(VIII)

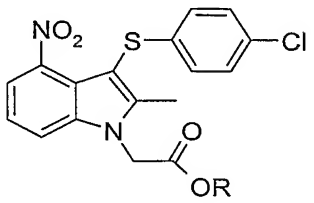
in which R is hydrogen or is as defined in formula (II) by reacting with a compound of formula (VII).



(VII)

in which R^1 is chloro or a group that can be converted to chloro, and optionally thereafter forming a pharmaceutically acceptable salt or solvate.

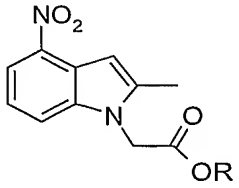
11. A process for the preparation of a compound of formula (II) or the corresponding carboxylic acid which comprises reducing a compound of formula (III):



(III)

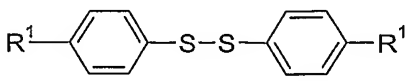
in which R is hydrogen or is as defined in formula (II) with sodium dithionite or by hydrogenation followed by amide formation.

12. A process for the preparation of a compound of formula (III) or the corresponding carboxylic acid which comprises reaction of a compound of formula (IX):



(IX)

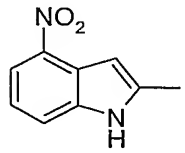
in which R is hydrogen or is as defined in formula (II) with a compound of formula (VII):



(VII).

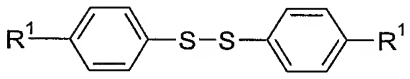
in which R^1 is chloro or a group that can be converted to chloro.

13. A process for the preparation of compounds of formula (IV) by reacting compounds of formula (VI):



(VI)

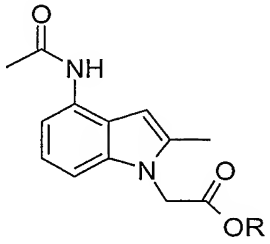
with compounds of formula (VII):



(VII)

in which R^1 is chloro or a group that can be converted to chloro.

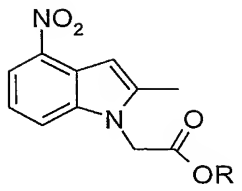
14. A compound of formula (VIII):



(VIII)

in which R is hydrogen, phenyl, benzyl or C_{1-6} alkyl.

15. A compound of formula (IX):



(IX)

in which R is hydrogen, phenyl, benzyl or C_{1-6} alkyl.

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(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; Astrazeneca AB, S-151 85 Södertälje (SE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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— *with international search report*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL PROCESS FOR THE PREPARATION OF SUBSTITUTED INDOLES

(57) Abstract: The invention relates to a novel process for the preparation of substituted indoles which are useful as therapeutic agents.

WO 2006/075139 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/000060

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/106302 A (ASTRAZENECA AB; BONNERT, ROGER; RASUL, RUKHSANA) 9 December 2004 (2004-12-09) cited in the application p. 30, example 5 i)claim 11	1-15

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 June 2006	17/07/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Wolf, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2006/000060

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004106302 A	09-12-2004	AU 2004242624 A1	09-12-2004
		BR PI0410711 A	13-06-2006
		CA 2526866 A1	09-12-2004
		EP 1656346 A1	17-05-2006